Typical and atypical development of functional brain networks in children

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Chapter 1

General introduction

The brain is a complex communication network. Undisturbed development of this immense network - consisting of trillions of connections between billions of neurons - is of great importance for healthy functioning later in life. During typical development major anatomical and functional changes occur *within* brain regions, which lead to specialization of these regions. Importantly, concurrent with these ongoing region-specific changes, connectivity and communication *between* regions develop and improve as well, which leads to better exchange and integration of information between regions. How these developmental changes ultimately lead to an efficiently organized network on which higher order cognitive functions can be acquired in childhood, or how this process might be disturbed during atypical development are important questions in developmental neuroscience that largely remain unanswered. Finding answers to these questions might give new insight in 'critical' stages of healthy development and periods during which children might be more vulnerable to 'environmental' stress. Moreover, it might lead to better understanding of disease mechanisms underlying neurodevelopmental disorders such as for instance autism and support clinical diagnosis at these early developmental stages when intervention may be most effective. In this thesis, both healthy and atypical development of functional brain networks is explored.

In this introductory chapter, first a short background is given on imaging of the brain as a complex communication network, then a short background is given on healthy brain development and atypical brain development in a group of children who are born small for gestational age (SGA) and a group of toddlers with autism, ending with a layout and the aims and outline of this thesis.

1.1 IMAGING BRAIN ACTIVITY AND FUNCTIONAL CONNECTIVITY

In this section, the basics of brain imaging methods will be introduced, to better understand how brain networks communicate during resting-state or during a task condition with an emphasis on neurodevelopmental aspects. A background will be given on how neuronal activity in the brain can be measured non-invasively from outside the brain with several

imaging techniques. Subsequently, functional connectivity is introduced and how networks can be constructed, followed by an introduction on graph analysis and how this approach can characterize the organization of functional brain networks.

1.1.1 EEG, MEG and fMRI

Neuronal activity gives rise to oscillating electromagnetic fields that can be recorded directly outside the head with electroencephalography (EEG) / magnetoencephalography (MEG). EEG detects the electric component, while MEG records the magnetic component of these fields. These signals originate from synchronized neuronal activity mostly within cortical brain regions underlying the EEG electrodes or MEG sensors. The amplitude of these oscillatory signals depends on the number of neurons firing in synchrony, which in turn depends on the local connectivity patterns between excitatory and inhibitory neurons as well as on local synaptic density and thalamic input. Thus, in response to changes of input, both the amplitude of the signal as well as the frequency of the oscillatory activity can change, and the frequency is often related to the transmission time of a signal coming from a different brain area, i.e. low frequencies modulate activity over large spatial regions and high frequencies modulate activity over small spatial regions (Von Stein and Sarnthein, 2000; Womelsdorf and Fries, 2007). For instance slow wave activity, such as in delta (1-4 Hz), theta (4-8 Hz) and alpha (8-13 Hz) frequency bands, has been associated with internalizing functions such as decision making, motivation, preparation and memory functions, filtering out irrelevant information, whereas oscillations with higher frequencies, such as beta (12-30

Glossary I

Oscillations: 'brainwaves' of repetitive or rhythmic variation in neural activity, which originate from local neuronal populations generating a fluctuating detectable electric (magnetic) field. The neural oscillator is periodically deviating from and recurring to its original state.
Amplitude: a measure for the instantaneous magnitude of the difference between the extreme values or peaks for an oscillatory waveform.
Phase: a measure for the position of the brainwave with reference to its origin.
Frequency: number of neural oscillations per second. Typically, neural oscillations are subdivided in delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (>30 Hz) bands.
Synchronization: coordination of neural activity between two or more brain regions that operate in unison.

Hz) and gamma (>30 Hz) band activity have been related to externalizing functions such as motion and attention selection (Canolty and Knight, 2010; Engel et al., 2001; Fries, 2005).

In addition to EEG and MEG methods, neuronal activity (as coupled to metabolic activity) can be measured indirectly by functional magnetic resonance imaging (fMRI), which quantifies blood oxygenation level dependent (BOLD) fluctuations in the brain (0.01 - 0.1 Hz) induced by fluctuations in neuronal activity (Biswal et al., 1995; Greicius et al., 2003).

1.1.2 Functional connectivity

In addition to the measures of local synchronization *within* brain regions underlying an EEG or MEG sensor described above, measures for synchronization *between* different brain regions can be computed and are important for characterizing the strength of communication or integration of information between all possible combinations of brain regions. A functional connection between two brain regions can be measured by computing the statistical correlations or interdependencies between the time series generated by two separate brain regions (Figure 1). In this thesis, the synchronization likelihood (SL) (Stam and Van Dijk, 2002) and the phase lag index (PLI) (Stam et al., 2007a) were computed as non-linear measures for functional coupling between brain regions. In short, the SL searches recurrences of patterns within a time signal and subsequently calculates the likelihood that in two separate time signals the recurrences of these patterns within the time series occur at the same time in both time series [Montez et al., 2006]. PLI reflects the consistency with which one signal is phase leading or lagging with respect to another signal. An advantage of this latter measure is that it is less sensitive to volume conduction and signals originating from common sources or an active reference in the case of EEG.

Furthermore, fMRI based resting-state functional connectivity was characterized with independent component analysis (ICA). This method is a data-driven multivariate analysis that decomposes temporal changes in 3D brain volumes into a set of spatial maps of distinct brain regions (components) with similar temporal patterns (co-fluctuations of the BOLD signal) (Beckmann et al., 2005; Calhoun et al., 2008; McKeown et al., 1998). The brain areas found within one component are assumed to have a strong functional coupling within one resting state network (RSN).

1.2 FUNCTIONAL BRAIN NETWORKS AND GRAPH THEORY

Why should we study the brain as a network? To gain new insight in how communication is organized in the brain network, understanding the parts or the sum of the parts of the brain is not sufficient. Important information lies within the complexity and organization of the connections of the network. By applying graph theoretical methods (a graph is a mathematical representation of a network) new insights can be revealed in how communication is organized in the brain. It offers a solution for the problems with measuring large numbers of connections, which leads to difficulties with statistical analysis (correction for multiple comparisons) and it furthermore leads to new insight and interpretation of the complex connectivity patterns itself. Many studies have previously addressed these problems by focusing/narrowing down on a selection of connections between regions of interest. In this way, potentially interesting effects in connections that were not considered in the analysis might have been missed. Graph analysis has been introduced to offer a solution to these problems as it captures the topology of the network in a few graph measures that give insight in the efficiency of the network organization.

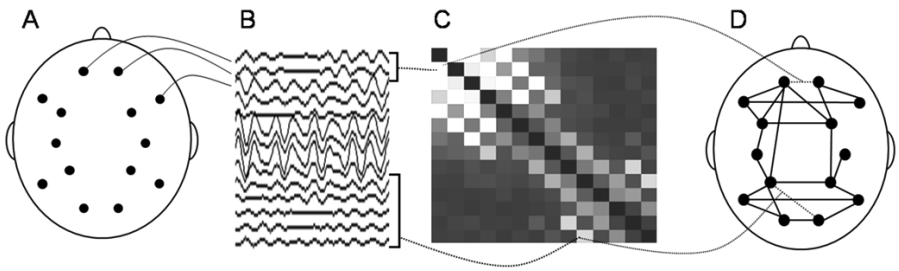

Figure 1. Schematic flow chart for functional network construction. (A) Top view of EEG recordings from several electrodes (black dots). (B) Time series are filtered in a frequency band of interest and (C) for all combinations of brain regions a measure for functional connectivity is calculated and stored in a matrix. (D) Schematic representation of a functional brain network representing only the strongest connections.

1.2.1 Constructing functional brain networks

To apply graph analysis to brain networks, the first step is to construct networks. The nodes of the network are represented by brain regions (or at a sensor level represented by EEG electrodes or MEG sensors), and the correlations between the time series measured from these nodes represent the functional connections of the network. In this way, a fully connected network can be constructed. When all the correlation values or weights of the connections are considered, the network is called a weighted network. One can also choose to construct a sparser connected or binary network by setting an arbitrary threshold to the weighted network thereby excluding the weakest functional connections. However, this can have consequences for network density and comparing network topologies under different experimental or clinical conditions. Connection weights might differ under different circumstances and setting a threshold might lead to including less or more connections for analysis. Both the number of nodes as well as the number of connections influence topological characteristics, thus network size does matter (Joudaki et al., 2012; van Wijk et al., 2010). Constructing networks with a similar number of links (and similar number of nodes) might present a solution to this network comparison problem. The minimum spanning tree (MST) is an approach that searches for the strongest links connecting all nodes of the network without forming loops or triangles. In this way, both the number of nodes and connections are maintained equal, thereby improving comparison of the topological characteristics under different conditions.

Glossary II

Graph: mathematical representation of a network.
Weighted network: a network in which the links between all nodes have weights assigned to them.
MST: minimum spanning tree; a method that searches for the strongest links to form a sub graph that connects all the nodes of the network without forming loops.
Nodal Degree: the number of links connected to a node.
Network Density: total number of connections included in the network.
Clustering: measure for the fraction of neighbors of nodes that are also neighbors of each other and it reflects local efficiency or functional segregation or specialization.
Path length: measure for the average of all shortest paths between any combination of nodes reflecting global efficiency of the network.
Modularity: degree to which a network can be subdivided in modules, i.e. highly connected subsets of nodes (modules) that are less connected to the rest of the network.

After network definition, the spatial the topology of the brain network can be characterized with several graph measures. In the next section, a background is given on graph analysis and how it can assist in characterizing and interpreting complex brain network organization.

1.2.2 Graph theory

The spatial organization or topology of the links connecting the nodes in a network is crucial for communication efficiency of the network. Networks can be classified as ordered, random, small-world, scale-free or modular networks, having different topologies and different qualities. For instance, ordered networks are characterized by a high local clustering (Figure 2A), which is the probability that the neighbors of a node are interconnected as well, leading to high efficiency of local information transfer. However, these ordered networks show a long characteristic path length which is the smallest number of steps (or the shortest distance) between any two nodes averaged for all possible combinations of nodes (Figure 2A) and leading to a low efficiency of information transfer globally over the network. By contrast, random networks show low clustering resulting in low local efficiency however they have a short characteristic path leading to high efficiency of information transfer globally. Interestingly, when a small fraction of links in ordered nearest neighbor network is randomly rewired, short cuts are created and the path to reach any node in the network is drastically shortened while local efficiency remains high, an important finding by Watts and Strogatz (Watts and Strogatz, 1998). Due to both a high clustering and short paths between clusters, these so-called *small-world networks* show an optimal balance between both local and global information processing in the network (Achard et al., 2006; Latora and Marchiori, 2001; Stam et al., 2007b). Another class of networks are the scale free networks which are characterized by a few 'hub'-like nodes that connect to many other nodes and many low degree nodes connecting to few other nodes. The degree (*k*) of node is the number of connections that exist between that node and other nodes. The skewed distribution of nodal degree (following power law) is essential to scale free networks. These networks show on the one hand highly efficient information integration via critical (high degree) nodes to which new nodes preferentially attach

(Barabasi and Albert, 1999). Whereas these networks show robustness for random attack, these networks are less robust to targeted attacks as damage of critical nodes as it will immediately result in failure to integrate information between all nodes. The final class described here, are modular networks (Figure 2B) which are characterized by highly connected subsets of nodes (modules) that are less connected to the rest of the network. These networks have high clustering, short paths leading to both local and global efficient information transfer and moreover, information integration remains efficient when nodes are randomly attacked, making this class of modular networks more resilient against random attack than the classes of networks described above. The next section will give a short overview of the findings of recent studies that investigated anatomical and functional brain networks from a graph theoretical perspective.

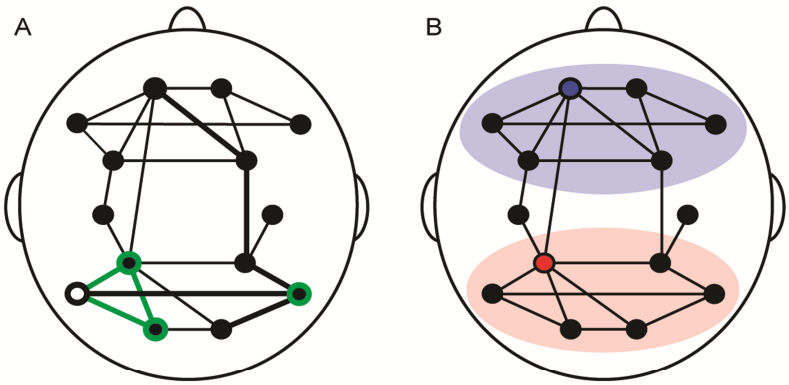

Figure 2. Illustration of measures for network topology. (A) Green nodes represent neighboring nodes of the white node (nodal degree =3). One out of three possible connections between neighbors is present leading to a clustering of 1/3. Dashed line represents the shortest path between any two nodes in the network. (B) Light blue and pink blobs represent two separate modules. Blue node plays an important role for communication within the module and red node is crucial for communication between modules.

1.2.3 Networks in the brain

What do we already know about the organization of brain networks? Recent studies have found that adult large scale brain networks show highly efficient small-world organizations

(Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010; Reijneveld et al., 2007; Sporns et al., 2004), characterized by a high clustering and short path length assuring an optimal balance between local segregation and global integration of information in the brain. Moreover, the path length of the brain network and intelligence are inversely related in healthy adults, indicating that more efficient topologies (i.e. shorter paths) favor cognitive performance (Douw et al., 2011; van den Heuvel et al., 2009; Li et al., 2009; Micheloyannis et al., 2005). The opposite has been found in several clinical studies on for instance Alzheimer's disease, schizophrenia or epilepsy demonstrating significant deviations in clustering, path length and, modularity (Bassett and Bullmore, 2009; de Haan et al., 2012; Fornito et al., 2012; Rubinov et al., 2009; Van Dellen et al., 2009), suggesting departure of the 'normal' optimal network topologies found in healthy controls. Interestingly, a high heritability of graph parameters has been found (Fornito et al., 2011; van den Heuvel et al., 2012; Smit et al., 2008) which might point to an (at least partially) important role for candidate genes that guide the development or outgrowth of efficiently organized brain networks. The studies described above mainly focused on brain networks in adults. An important question that remains to be answered is how the organization of functional brain networks is characterized in young children and more specifically how the topology of these networks changes during typical and atypical brain maturation.

To answer these questions in this thesis, brain networks were studied groups of normally developing subjects, and atypical development was studied in a group of children that were born small for gestational age and in children with autism at very early developmental stages. In the next section a short description and background of the study populations will be given.

1.3 TYPICAL AND ATYPICAL BRAIN DEVELOPMENT

To gain insight in what goes wrong during restricted or disturbed development, better understanding of healthy typical brain development is required. Healthy brain development is highly complex in itself. Different brain regions start to develop at different moments

prenatally, and every region has its own developmental trajectory of growing neurons and connections. Box 1 gives a short summary and general overview of typical brain maturational processes at the micro scale.

Typical functional brain development at a macro scale has been characterized in several ways. Local activity *within* brain regions, i.e. synchronization of the underlying local neuronal networks, can be characterized by a reduction in the amplitude of slow oscillations (1-8 Hz) and increases in the amplitude of high frequency oscillations (8-35 Hz) (Clarke et al., 2001; Okumura et al., 2006) suggesting an acceleration of brain oscillations during healthy development. Interestingly, development of communication *between* brain regions has been characterized by a reduction of synchronization over short distances and increased synchronization over long distances with typical brain maturation (Barry et al., 2004; Fair et al., 2007, 2009; Hagmann et al., 2010, 2010; Kelly et al., 2009; Thatcher et al., 2008; Uddin et al., 2010). Thus, developmental changes in specific connections are complex and widespread and need further investigation to better understand how the brain is

BOX 1. Brain development at early age

Typical brain development at the micro scale is characterized by abundant growth of neurons in the first trimesters and in the third trimester this proliferation and migration of neurons is completed while, in the same period, connections between neurons start to be formed via synaptogenesis and dendritic aborization [Huttenlocher, 1984]. Early in postnatal life, axons that connect neurons over long distances and provide the routes for communication between more distant brain regions, start to be myelinated, leading to improvement of the signal transfer between distant neurons, a process that continues well into the fourth decade of life [Lebel et al., 2008; Tamnes et al., 2010; Yap et al., 2011]. Simultaneously, superfluous synaptic connections start to be pruned, following a 'use it, or lose it' principle and many neurons vanish by apotosis (programmed cell death) [Huttenlocher 1984; Volpe 2000; Flavell and Greenberg 2008]. These maturational processes at the micro scale lead to changes at the macro scale which can be measured by magnetic resonance imaging (MRI). As such, cortical grey matter volumes (predominantly containing cell bodies of neurons and local synaptic contacts) have been found to increase in the first postnatal years, presumably due to increased numbers of neurons and connections. Subsequently, this thickening of the cortex is reduced and eventually followed by decreases in grey matter volumes due to pruning of exuberant connections and apoptosis (programmed cell death) of neurons. In general, this grey matter thinning starts from the back of the brain and moves to the front of the brain. Concurrently, white matter volumes and integrity is starting to increase leading to improvement signal guidance over (bundles of) connections between more distant regions which continues into the third decade of life [Giedd et al., 2009; Marsh et al., 2008; Wilke et al., 2007].

changing at the system level, as a complex interacting network that integrates information between specialized brain regions.

A risk factor for disturbed brain development might be restricted intra-uterine growth. This can result in diminished body weight and length and decreased head circumference at birth, which has been described in children being born small for gestational age (SGA) (De Bie et al., 2010; Frisk et al., 2002; Mallard et al., 2000; Rehn et al., 2004; Saenger et al., 2007; Toft et al., 1995; Tolsa et al., 2004). Of all live-born neonates, a small percentage is born SGA which is defined as a birth weight and/ or length ≤ -2 standard deviations (Lee et al., 2003). Approximately 10 % of these SGA born children lack catch-up growth (SGA-) showing persistent short stature, while the majority of the SGA born children shows catch-up growth in the first two years of life (SGA+) (Saenger et al., 2007). Being born SGA is associated with decreased levels of intelligence and cognitive abilities (De Bie et al., 2010; Strauss, 2000), and, interestingly, spontaneous bodily catch-up growth during the first two years of life has been associated with better cognitive outcomes (Frisk et al., 2002; Lundgren et al., 2001; Saenger et al., 2007). Hence, an important and partly unanswered question is how growth restriction early in life affects functional brain development. Since frequent monitoring of fetal growth with ultrasound echo is not a common procedure, the period during which SGA born children suffered from intra-uterine growth restriction is generally unknown. The timing of this early life growth restriction can affect several brain maturation processes (see BOX 1), which might have consequences for brain development on the long-term. One of the known effects of being born SGA on brain development later in life, is the reduction of white matter volume found in 15-year-old adolescents when compared to healthy adolescents (Martinussen et al., 2005, 2009). More recently, comparable effects of being born SGA on brain volumes have been found in children (De Bie et al., 2011), demonstrating smaller brains with lower white matter volumes and a smaller cortical surface area in SGA born children of school age. This study additionally differentiated between SGA born children who showed spontaneous postnatal catch-up growth (SGA+) and who lacked this catch-up growth (SGA-) and found a linear trend ordered from highest volumes and surface area in AGA via SGA+ to SGA- children. Besides anatomical deviations, aberrant brain activity has been found in SGA born neonates

(Ozdemir et al., 2009) indicating a developmental delay in these neonates. Thus, both anatomical and functional brain deviations are found in SGA born children and a favorable effect of postnatal catch-up growth was suggested. One of the aims of this thesis was to explore whether and if so, how growth restriction at early stages of development affects brain activity and communication on functional network organization in SGA born children at school age.

Autism is a neurodevelopmental disorder that is characterized by communication and language deficits, impaired social interactions, stereotyped and restricted behavior and atypical sensory sensitivity, and these symptoms emerge already in the first years of life. Atypical brain maturation is hypothesized to occur at very early developmental stages in autism. More specifically, a deviant anatomical growth pattern with accelerated brain development in the first years and a subsequent decline in growth around the age of four has been theorized in autism (Courchesne et al., 2001; Wass, 2011). However, the underlying neurophysiological deficits at these early stages are not well understood yet. Previous studies mostly in adults, have found heterogeneous patterns of deviant functional brain connectivity in autism, which frequently have been summarized or interpreted as local over connectivity and global under connectivity (Just et al., 2012; Kana et al., 2011; Muller et al., 2011; Murias et al., 2007; Vissers et al., 2012; Wass, 2011). One graph theoretical study in adult patients with autism reported reduced levels of absolute clustering and longer absolute characteristic path length in EEG based networks, which was suggested to reflect inefficient local and global topology of the brain network in adult patients (Barttfeld et al., 2011; Khan et al., 2013; Peters et al., 2013). In a group of toddles with a diagnosis of autism a general pattern of disrupted synchronization in the spontaneous slow fluctuating cortical activity (measured with fMRI) (Dinstein et al., 2011). Despite these studies, our knowledge of the underlying organization of functional brain networks at an early and crucial stage of brain development remains limited. Therefore, investigating the brain dynamics at these early developmental stages is crucial for gaining new insight in deviant brain development in autism.

1.4 STUDY POPULATIONS

Typical brain development in children was studied using a dataset which was previously collected in a study of genetic and environmental influences on neural development during childhood conducted in twins at 5 (M = 5.2 years, SD = 0.2) and 7 years of age (M = 6.8, SD = 0.2) (Van Baal et al., 1996; van Baal et al., 2001). The twins were all registered at the Netherlands Twin Register (Boomsma et al., 1992, 2006). All participants were healthy with normal IQ (Boomsma and Van Baal, 1998). For the studies on development in children (Chapter 2 and 3), we only included children with an EEG measurement both at 5 years of age and a repeated measurement at 7 years of age.

Brain maturation throughout the life span was studied in datasets that were previously collected as part of an ongoing study into the genetics of brain development and cognition. Six groups with ages centered around 5, 7, 16, 18, 25, and 50 years were included. Part of these datasets consisted of longitudinal measurements at two ages (5–7 and 16–18 years). In addition, some of the subjects aged 16–18 years were invited back for measurements at age 25.

Atypical brain development was studied in children who were born SGA (Chapter 5, 6 and 7) and in children with autism (Chapter 8). The studies in SGA born children examined baseline data collected in a longitudinal project studying the effects of growth hormone therapy on cognition and brain development in children born SGA (Dutch Trial Register NTR 865). This complete project included neuropsychological assessment, MRI, and MEG investigation and was performed at the VU University Medical Center. SGA born children were selected from the pediatric hospitals in The Netherlands. Most of the AGA children were acquaintances of the SGA children; the remainder was recruited via staff members of the study project. Inclusion criteria for AGA, SGA+ and SGA- are: 1) gestational age ≥ 34 weeks, 2) single birth, 3) history without complicated neonatal period with signs of sever asphyxia, defined as an Apgar score ≥ 7 after 5 minutes, 4) no growth failure due to other somatic of chromosomal disorders or syndromes (except for Silver Russell syndrome), 5) no previous or present use of medication that could interfere with growth or with growth hormone treatment, 6) body containing irremovable metal parts, 7) no severe learning

disability (no IQ< 70). SGA born children who met the criteria set by the International Small for Gestational Age Advisory Consensus Board Development Conference Statement were included (Lee et al., 2003): SGA was defined by a birth weight and/or length ≤ -2 SD, adjusted for gender and gestational age; SGA+ was defined as postnatal catch-up growth with an actual height of less than 2 SD below the Dutch population reference mean; and SGA- as persistent postnatal growth failure based on an actual height of less than 2.5 SD below this mean (Fredriks et al., 2000). Additionally, being born appropriate for gestational age (AGA) was defined as birth weight and length above - 2 SD, without known history of prenatal growth restriction. All children were born term (>35 weeks).

The study in children with autism presents data collected previously from patients who were recruited from the Department of Psychiatry of the University Medical Center in Utrecht, and from Karakter Child and Adolescent Psychiatry University Center in Nijmegen. A group of twelve children (mean age 3.35 y ± 0.80; IQ= 85.0 ± 17.2) with a clinical diagnosis of autism spectrum disorder (ASD) according to DSM-IV criteria were included in this study. The group of patients received a clinical diagnosis according to DSM-IV criteria of Autism (2 patients), Asperger Syndrome (1 patient) or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS; 9 patients). Nineteen control children (mean age 3.53 y ± 1.19; IQ = 108.0 ± 12.4) participated and were recruited from different schools and child care centers in the Utrecht area. To exclude clinically relevant psychopathology among the control children, the parents completed the Child Behavior Checklist (CBCL/1.5-5) (Achenbach and Ruffle, 2000), and the Vineland Social-Emotional Early Childhood Scales (Carter et al., 1998) were administered. All children scored within the normal range of the CBCL and Vineland scales and were included for further analysis.

1.5 RESEARCH QUESTIONS, AIMS AND OUTLINE

1.5.1 Research questions

The main research question of this thesis is: How are functional brain networks organized in young children during typical and atypical development of the brain? More specifically, we addressed the question whether typical brain development is related to shifts in brain network organization over time and if so, how these shifts are characterized in typical development? Additionally, as sex hormones are known to have a strong influence on brain development, the question whether boys and girls differ in functional brain network organization was addressed.

The second main question was aimed at atypical brain development. We examined children who were born small for gestational age (SGA) and explored whether these SGA born children develop different brain functional networks compared to children who were born appropriate for gestational age (AGA). Furthermore, atypical development of brain functional networks was studied in children with autism to examine if this neurodevelopmental disorder leads to deviant brain organization already at a very early age of development.

1.5.2 General aim

The general aim of this thesis was to explore and better understand and how functional brain networks are characterized in young children and how network topology evolves during typical and atypical brain development with the use neuroimaging and graph theoretical analysis.

1.5.3 Specific aims and methods

To explore typical development of the organization of functional brain networks based on EEG and fMRI data of healthy developing individuals:

- spectral analysis
- functional connectivity analysis
- graph analysis based on weighted networks and minimum spanning trees

- independent component analysis

To explore whether and if so how atypical development leads to disruption of the organization of functional brain networks based on MEG and EEG data of children born SGA and toddlers with autism:

- spectral analysis
- functional connectivity analysis
- graph analysis based on weighted networks

1.5.4 Outline

In this thesis the effect of typical development on EEG based functional brain network organization is explored and described in Chapter 2, 3, and 4. **Chapter 2** describes the change in functional brain network topology during typical development in young twins. In **Chapter 3**, the minimum spanning tree method is introduced and applied to support our hypothesis on development changes in functional brain network organization. **Chapter 4** describes shifts in functional brain networks network organization during typical maturation over the full life span.

In Chapters 5, 6 and 7 the focus was on atypical development of brain functional networks in SGA compared to AGA born children, based on MEG and fMRI measurements. The effect of being born SGA on local brain activity was investigated by a spectral power analysis on a resting-state MEG data in **Chapter 5**. Additionally, in **Chapter 6**, global brain activity was further explored by graph analysis of MEG based resting-state functional network in SGA born children. **Chapter 7** describes resting-state fMRI networks in a combined group of five- to eight-year old SGA and AGA born children. Disruption of functional brain networks based on EEG data in toddlers with autism was investigated in **Chapter 8**. Finally, in **Chapter 9** the most important findings are summarized and discussed and some directions for future studies are suggested.

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